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Patient-reported Symptoms of Tenosynovial Giant Cell Tumors

Heather L. Gelhorn, PhD[1], **Sandra Tong, MD**[2], **Kelly McQuarrie, BS**[1], **Christina Vernon, MPH**[1], **Jennifer Hanlon, MPH**[1], **Grant Maclaine, BMedSc, MBBS, MEc, MA**[3], **William Lenderking, PhD**[1], **Xin Ye, PhD, MS**[4], **Rebecca M. Speck, PhD, MPH**[1], **Richard D. Lackman, MD**[5], **Susan V. Bukata, MD**[6], **John H. Healey, MD**[7], **Vicki L. Keedy, MD, MSCI**[8], **Stephen P. Anthony, DO**[9], **Andrew J. Wagner, MD, PhD**[10], **Daniel D. Von Hoff, MD**[11], **Arun S. Singh, MD**[6], **Carlos R. Becerra, MD**[12], **Henry H. Hsu, MD**[2], **Paul S. Lin, MD, MBA**[2], and **William D. Tap, MD**[7]

[1]Evidera, Bethesda, Maryland [2]Plexxikon Inc, Berkeley, California [3]Daiichi Sankyo Development Ltd, Buckinghamshire, United Kingdom [4]Daiichi Sankyo Pharma Development, Edison, New Jersey [5]Cooper University Health Center, Orthopaedic Oncology Center, Camden, New Jersey [6]Ronal Reagan UCLA Medical Center, Los Angeles, California [7]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, New York [8]Vanderbilt University Medical Center, Hematology/Oncology, Nashville, Tennessee [9]Texas Oncology-Tyler, Tyler, TX [10]Dana-Farber Cancer Institute, Boston, Massachusetts [11]HonorHealth & Translational Genomics Research Institute, Scottsdale, Arizona [12]Sammons Cancer Center/US Oncology, Dallas, Texas

Abstract

Purpose—Tenosynovial giant cell tumor (TGCT), a rare locally aggressive neoplasm of the synovium of joints and tendon sheaths, is associated with joint destruction, inflammation, pain, and swelling, in part due to colony-stimulating factor 1 receptor–bearing macrophages recruited to the tumor by genetic elevation of colony-stimulating factor 1 activity. The most common treatment is surgery, although promising pharmacologic treatments are in development. Patient-reported outcome (PRO) instruments are critical end points in demonstrating the clinical relevance of standard oncologic outcome measures and the overall impact of novel pharmacologic therapies in nonmalignant neoplastic conditions such as TGCT. The content validity of PROs relevant to patients with TGCT has not been formally investigated, and instruments to evaluate such outcomes do not exist for this condition.

CONFLICTS OF INTEREST

G. Maclaine and X. Ye are employees of Daiichi Sankyo Development Ltd, which provided financial support for this research. S. Tong and P. Lin are employees of Plexxikon Inc, which provided financial support for this research. J.H. Healey is a paid consultant of Daiichi Sankyo Development Ltd. H. Hsu is a paid consultant of Plexxikon Inc. S. Anthony is a paid member of the Paradigm Medical Evidence Team and a paid consultant of Zymeworks Biopharmaceuticals. W. Taq is a paid consultant of Plexxikon and Daiichi Sankyo Development Ltd. The institutions of S. Bukata, D. Von Hoff, and V. Keedy received funding from Plexxikon for conducting the study for this work. D. Von Hoff is a paid consultant of Five Prime Therapeutics. H. Gelhorn, K. McQuarrie, C. Vernon, J. Hanlon, W. Lenderking, and R. Speck participated in this project as employees of Evidera, a company which performs work for hire for multiple pharmaceutical and device companies in outcomes research. K. McQuarrie is currently employed by Janssen. A. Wagner, A. Singh, C. Becerra, J. Hanlon, and R. Lackman have no conflicts of interest related to this work to report.

Methods—PRO instruments of potential relevance were evaluated by using a literature review and by clinical and PRO experts. Patients with TGCT were recruited through clinical sites and the Internet for participation in qualitative research interviews to identify predominant symptoms and to test the relevance and content validity of several PRO measures. Select PRO measures were included in a Phase I clinical trial, and preliminary results of the PRO end points are reported descriptively.

Findings—Of the 22 subjects who participated in qualitative interviews, 73% were female, and their mean age was 42.5 years (range, 27–56 years). The TGCTs (19 diffuse and 3 localized) were located in the knee (n = 15), hip (n = 3), ankle (n = 2), elbow (n= 1), and forearm (n = 1). The most common symptoms cited were pain (82%), swelling (86%), stiffness (73%), reduced range of motion (64%), and joint instability (64%), which were consistent with clinical expert input and with the content of instruments chosen by PRO experts. The worst pain numeric rating scale, Patient Reported Outcomes Measurement Information System physical functioning items, and the Western Ontario and McMaster Universities Osteoarthritis Index, as well as a worst stiffness numeric rating scale developed for TGCT, were confirmed as meaningful measures of TGCT patient symptoms and were well understood in qualitative interviews. Results from the Phase I trial showed trends of improvement in both pain and stiffness over time.

Implications—This study is the first to gather information directly from patients with TGCT regarding their symptom experiences. Pain, stiffness, and physical functioning are important treatment outcomes in patients with TGCT. We have identified content-valid PRO measures of these concepts, which are included in an ongoing Phase III TGCT clinical trial with pexidartinib (PLX3397) (NCT02371369).

Keywords

pigmented villonodular synovitis (PVNS); giant cell tumors of the tendon sheath (GCT-TS); tenosynovial giant cell tumor (TGCT); patient-reported outcomes (PRO); PROMIS

INTRODUCTION

Pigmented villonodular synovitis (PVNS) and giant cell tumors of the tendon sheath (GCT-TS) are members of a single condition referred to as tenosynovial giant cell tumor (TGCT), localized and diffuse type, and have a common pathogenesis.[1] They are proliferative neoplasms involving the synovium and tendon sheaths that typically present in young and middle-aged adults of both sexes. Diffuse-type TGCT tends to be more aggressive, often recurring locally (8%–56%) after surgery, and is capable of malignant transformation.[2] In a retrospective analysis of 49 previously untreated patients with PVNS of the knee (12 localized, 37 diffuse), the overall relapse rate after surgery was 43%, with 52% of diffuse-type relapsing within 5 years.[3]

Although rare, TGCTs are likely underreported and underdiagnosed, with an estimated overall annual incidence in the United States of 11 cases per million, including ~1.8 cases per million for PVNS, and 9.2 cases per million for GCT-TS.[4] More recent nationwide pathology data from the Netherlands estimate the annual incidence of TGCTs to be 49.7 cases per million.[5]

The current standard of care for TGCT is surgical resection of the tumor as completely as possible to reduce symptoms and joint destruction, improve function, and minimize the risk of recurrence.[6] Although surgery is the standard of care, it has been observed that expression of the colony-stimulating factor 1 gene is elevated in most TGCT tumors[7] and may, in many cases, be driven by a gene translocation.[8,9] This possibility has led to the development of therapies targeting the colony-stimulating factor 1 receptor for which regression in tumor volume is the primary indicator of response.[10]

For both clinicians and regulators to evaluate the relevance of treatment effects for patients, it is critical to understand the symptoms that patients experience and whether tumor shrinkage improves these symptoms and patients' health-related quality of life. Although tumor volume is a critical end point of new therapeutic agents, patient-reported outcome (PRO) instruments inform the clinical relevance of standard oncologic end points and treatment benefits from the patient perspective. PRO data are essential to understand the appropriate clinical application of a targeted therapy in this neoplastic condition with varying clinical sequelae. This is particularly true for TGCT, a rarely lethal but morbid tumor, in which the duration of systemic therapy is likely to be much longer with a more lengthy window of exposure to toxicities, compared with malignant tumors in which the duration of exposure to systemic agents is limited by a patient's life span.[11]

There is a dearth of PRO research among patients with TGCT; to our knowledge, 3 studies have reported on PRO outcomes assessed in this population by using standardized instruments.[12–14] To date, symptom measures and other PROs relevant to patients with TGCT have not been formally researched, and PRO instruments validated among patients with TGCT do not currently exist. Thus, a qualitative interview study was completed to identify and characterize symptoms associated with TGCT and to evaluate several PRO instruments that could appropriately assess these symptoms in the context of a clinical trial.

PATIENTS AND METHODS

Overall Study Design

This study was designed to: (1) identify symptoms that are experienced by patients with TGCT; and (2) evaluate the content validity of several potentially relevant PRO instruments among patients with TGCT. The study consisted of a targeted literature review, interviews with clinical experts, and cross-sectional, qualitative semi-structured interviews with patients.

Select PRO instruments were identified, tested, and refined through the qualitative research with patients and were then incorporated into a Phase I trial (NCT01004861) to provide a preliminary evaluation of the feasibility and value of including these PRO measures as supportive end points. Specifically, the pain and stiffness numeric rating scale (NRS) PROs were included in a Phase I trial of pexidartinib (PLX3397), and the longitudinal trends in the results are summarized descriptively.

Background Research

Targeted Literature Review—Two searches of the peer-reviewed literature were conducted for publications describing relevant symptoms, PRO instruments, and/or information on the use of PROs in clinical trials. The first search was conducted to identify publications that included either clinical trials or case reports on TGCT. Because TGCT is a rare disease, the literature describing relevant PROs or supporting the psychometric properties of PROs in this patient population was expected to be sparse. Therefore, a second search was conducted in similar conditions including osteoarthritis, rheumatoid arthritis, and meniscal tears. These therapeutic areas were selected because the symptoms and difficulties associated with these conditions (ie, stiffness, swelling, pain, immobility) were expected to be similar to those experienced by patients with TGCT.

Clinical Expert Interviews—Four clinicians with expertise in treating TGCT participated in individual clinical expert interviews (S.V.B., J.H.H, R.D.L., and W.D.T.). The experts were asked for their input on: (1) the relevant symptoms and impacts reported to them by their patients with TGCT; (2) the proposed inclusion and exclusion criteria for the qualitative study; and (3) the potentially relevant PRO measures that had been identified through the literature review or that they additionally recommended for consideration.

Qualitative Interview Study

Participants—Due to the rare nature of the disease, a multimodal recruitment strategy was pursued. Participants were recruited either through a clinical site or identified through online activity (eg, blogging, Internet posts on disease-specific websites) as a potential person with TGCT. Individuals recruited through the Internet were asked to sign a release of medical information that was sent to their treating physician for confirmation of their diagnosis.

Participants were eligible for the study if they were able to participate in a 1-on-1 interview, were at least 18 years of age, had been diagnosed with PVNS or GCT-TS (active present tumor or previously treated tumor), were able to read and speak in English, and were willing and able to provide informed consent. Participants were ineligible if they had any significant impairment that could interfere with their ability to provide consent or participate in the interview, or if they had any systemic or local illness or medical condition that could interfere with the participants' perception of TGCT symptoms. This study was approved by a central institutional review board (Ethical & Independent Review Services; Protocol 13061), and all patients provided written informed consent.

Interview Procedures—The semi-structured interview guide for the qualitative study involving 1-on-1 in-person or telephone-based interviews was developed on the basis of results of the literature review and input from the clinical experts. The interview guide included 2 main parts. The first part involved concept elicitation to identify the key relevant symptom concepts and the effects of these symptoms as experienced by patients. Open-ended questions were included in the concept elicitation phase of the interview and were intended to capture a broad range of symptom and impact information from the patient perspective.[15] These initial questions asked participants to talk about the location of their tumor, the process of being diagnosed, treatments, the symptoms they had experienced

(description, frequency, variability, and relationship with pain), and effects they had noticed. The second part included a cognitive interview that was designed to have the patients provide feedback on the content and their understanding of several PRO instruments of potential relevance. This process included questions for each instrument, specifically probing participants about the relevance, instructions, item content, recall period, and response options. All interview discussions lasted ~90 minutes and were audio-recorded. At the conclusion of the interviews, the participants were asked to complete a sociodemographic and clinical form. Patients were remunerated for their participation.

Measures—Although 46 PRO instruments were identified as potentially relevant based on the background research (eg, Lysholm knee scoring scale, Knee Injury and Osteoarthritis Outcome Score, Short-Form 36), a subset of these PROs were selected for further evaluation in the qualitative study based on results of the literature review and clinical expert input. The selected instruments included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), symptom numeric rating scale (NRS) items (ie, pain, stiffness, swelling, immobility, limited motion), and the Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) items. The instruments were selected because they most closely and comprehensively captured the key symptoms and effects of TGCT as reported in the literature and by the clinical experts.

Western Ontario McMaster Arthritis–Pigmented Villonudular Synovitis and Giant Cell Tumor of the Tendon Sheath Index—The Western Ontario McMaster Arthritis–Pigmented Villonodular Synovitis and Giant Cell Tumor of the Tendon Sheath (WOMAC PVNS-GCTTS) index, used in the current study, is a modified version of the WOMAC Index NRS 3.1, a self-administered 24-item instrument assessing pain, stiffness, and difficulty performing daily activities originally designed for osteoarthritis.[16,17] The WOMAC is focused on assessing issues associated with lower extremity conditions, mainly the knee and hip. All items are measured on a 0- to 10-point NRS. The WOMAC PVNS-GCTTS asks the same questions as the original WOMAC but was adapted to specifically ask participants to consider the symptoms at the “study joint/tumor location.” This minor change to the WOMAC was approved by the instrument developer.

Symptom NRS Items—Patients were asked about pain, swelling, stiffness, instability, and limited motion using a series of 0- to 10-point NRS items. Adapted from the Brief Pain Inventory item that asks patients to rate their pain at its worst in the last 24 hours,[18] the NRS symptom items asked the participants to “Please rate your [insert symptom] by circling the one number that best describes your [insert symptom] at its worst in the past 24 hours.” The instructions indicated to participants that the questions were about symptoms at the site of their tumor. The anchors for the pain scale were labeled 0 = “no pain” and 10 = “pain as bad as you can imagine.” The scales for the other symptoms were anchored with 0 = “no swelling” (or “no stiffness”) and 10 = “worst imaginable.”

PROMIS-PF Assessment—The PROMIS-PF is an item bank comprising 121 self-administered items to assess physical functioning. The items focus on the functioning of one’s upper extremities (dexterity), lower extremities (walking or mobility), central regions

(neck and back), and instrumental activities of daily living.[19] All items include a 5-point response scale. For capability questions, the response scale ranges from “without any difficulty” to “unable to do.” For questions on limitations, the response scale ranges from “not at all” to “cannot do.” For the purposes of the present study, participants did not complete the full instrument; they were instead presented with a checklist of 121 PROMIS-PF items and were asked to indicate which items were relevant to them based on their experiences with TGCT. During the cognitive interview portion of the semi-structured interview, the patients were debriefed on 2 of the PROMIS-PF items that were selected because it was anticipated that they were likely to be relevant (ie, “Are you able to stand for 1 hour?” and “Are you able to do chores such as vacuuming or yard work?”)

Data Analysis—All interviews were audio-recorded and professionally transcribed, and then reviewed for accuracy and removal of any identifying information. A coding dictionary was developed based on the themes and concepts that emerged in the interviews. Coding of the words and phrases into key themes, attributes, concepts, and relationships was completed by using the constant comparative method,[20] an iterative coding approach that involves moving through transcripts consecutively and returning to previous transcripts as new codes emerge. The qualitative analysis was completed by using ATLAS.ti version 5.2 software.[21] Outputs from the coded transcripts were used to summarize the patient feedback in tabular format. Descriptive statistics (mean, SD, and frequency) for sociodemographic and clinical data were used to characterize the sample.

Phase I Study

An ongoing open-label, single-arm, multicenter, extension cohort of a Phase I trial of pexidartinib in TGCT (Tap et al[10] provides additional details) was amended to include the symptom NRS items at first dose and first day of each 4-week cycle; they were also collected at 6 days before each of these visits. Magnetic resonance imaging scans were evaluated for local Response Evaluation Criteria in Solid Tumors Version 1.1 assessment at screening and every 8 weeks (every other treatment cycle). The data cutoff date of the Phase I trial data that were analyzed and presented in this manuscript was July 31, 2015.

RESULTS

One-on-one in-person and telephone-based interviews were conducted with 22 participants who had a mean age of 42.5 years (range, 27–56 years); 73% (n = 16) were female. The locations of the participants’ tumors included the knee (n = 15 [68%]), hip (n = 3 [14%]), ankle (n = 2 [9%]), elbow (n = 1 [5%]), and forearm (n = 1 [5%]). Additional patient-reported sociodemographic and clinical characteristics are shown in Tables I and II, respectively.

Concept Elicitation

Participants described a range of symptoms in the concept elicitation portion of the interviews, many of them spontaneously in response to the open-ended questions at the beginning of the interview. Table III displays a summary of the concept elicitation results, both the spontaneously reported symptoms and those elicited through probing. Pain and

swelling were the most commonly reported symptoms, each mentioned by a majority (82% and 86%, respectively) of the participants. Stiffness (73%), reduced range of motion (64%), and joint instability or giving out/giving way (64%) were also commonly mentioned by participants.

In general, participants used similar words to characterize their experience of these symptoms and reported day-to-day and within-day variability in terms of presence/absence, frequency, and severity of the symptoms. An example participant quote is below.

> "It was a general pain. Sometimes I wouldn't feel it at all, but I especially felt it if I was to squat down. Then it just felt like, because of the tumors, that there was too much soft tissue in my knee and it wanted to expand out of the joint. It didn't necessarily look swollen to me, but it felt very full and swollen."

Cognitive Debriefing of PROs

WOMAC PVNS-GCTTS—Overall, participants with lower extremity tumors found the WOMAC PVNS-GCTTS to be highly relevant, easy to understand, and that the response options and recall period of 48 hours were appropriate. However, participants with upper extremity tumors reported that the entire WOMAC PVNS-GCTTS measure was not relevant to them. These upper extremity tumor participants did indicate that some of the other measures were relevant to them (ie, NRS and PROMIS).

Some specific findings on individual WOMAC PVNS-GCTTS items were noted. For example, the item "getting in and out of a car, or getting on or off a bus" was difficult for some participants to answer because it depended on the height of the vehicle. The 2 items related to socks ("putting on socks" and "taking off socks") were less relevant to approximately one third of the participants. In addition, there was considerable variability and some confusion regarding the interpretation of "heavy chores." Finally, about one half of the participants reported that they did not take baths (they took showers); thus, this item was not relevant to them.

Symptom NRS Items—All participants understood the symptom NRS items as intended and noted correctly that the questions were specific to the symptoms at the site of their tumor. Participants were able to respond to the questions with ease using the recall period and the response scale provided. The 24-hour recall period was confirmed as appropriate because many participants indicated that their experience of pain and stiffness in particular varied within this time frame.

PROMIS-PF Items—A total of 54 items from the PROMIS-PF item bank were identified as relevant by ≥20% of the study participants. Based on review of the PROMIS-PF item checklists and the qualitative transcripts for specific mention of effects on physical functioning, 15 PROMIS-PF items were identified that best captured the impact of TGCT on physical functioning. In addition to the relevance as endorsed by participants on the PROMIS-PF checklist, selection of the items was also strongly informed by the statements made by participants during both the concept elicitation and the cognitive debriefing portions of the qualitative interviews. These statements included whether the experience was

common, whether each item was sufficiently specific, and whether the impact/activity described was likely to occur frequently (eg, on a daily basis).

Of the 15 identified items, the PROMIS-PF checklist exercise revealed that 9 were endorsed as relevant to participants with either upper or lower extremity tumors (n = 22) (carry a laundry basket up a flight of stairs [45% of the participants indicated that this item was relevant on the PROMIS-PF checklist]; able to exercise for 1 hour [55%]; able to dress oneself [5%]; health limits going outside of home [14%]; able to push open a heavy door [36%]; able to carry a heavy object >10 pounds [41%]; health limits doing moderate work around the house [36%]; health limits doing heavy work around the house [50%]; and health limits lifting or carrying groceries [27%]). According to the PROMIS-PF checklist exercise, 4 items were relevant only to participants with lower extremity tumors (n = 20) (able to walk at least 15 minutes [40%]; able to stand for 1 hour [60%]; able to go up and down stairs at a normal pace [65%]; and health limits bending, kneeling, and stooping [60%]). Finally, there were 2 items endorsed as relevant during the PROMIS-PF checklist exercise that were unique to participants with upper extremity tumors (n = 2) (able to change a light bulb overhead [50%]; able to lift 10 pounds above one's shoulder [50%]). Several of these concepts, although endorsed by a smaller number of participants during the PROMIS-PF checklist exercise, were considered to be worthy of inclusion based on the results of the qualitative interviews in which additional participants noted that they were relevant.

These 15 physical functioning items from the PROMIS-PF item bank were used to create physical functioning measures specific to patients with either upper extremity tumors (11 items) or lower extremity tumors (13 items), including 9 items that overlapped across both scales. Because the PROMIS-PF item banks include information on the statistical properties of the items (ie, the item slope and thresholds) that have been estimated across the entire item bank by using item response theory, the physical functioning scores for each participant (regardless of tumor location) can be scored on the same physical functioning metric and analyzed together.

For the 2 PROMIS-PF items that were discussed specifically during the interviews (stand for 1 hour, and do chores such as vacuuming or yard work), participants' responses indicated that the items were understood as intended, and that the response options provided were acceptable.

Application of PRO Measures in a Phase I Trial

The pain and stiffness NRS measures were piloted in an ongoing, single-arm, extension cohort of a Phase I clinical trial of pexidartinib (NCT01004861). The patient population and primary results of the clinical trial have been previously reported.[10] Twenty-three patients with advanced TGCT were enrolled into the extension cohort and completed PROs at baseline and on-treatment. The mean age was 44 years, and 13 (56%) were female. The location of tumors was as follows: 12 (52%) knee, 5 (22%) hip/thigh, 3 (13%) ankle, and 1 (4%) each of elbow, forearm, and wrist; 1 patient with a knee lesion also had metastatic disease. Seventeen patients had undergone surgery previously; 1 patient had had prior radiation therapy.

Descriptive results of the mean change in the pain and stiffness NRS items from baseline through week 25 are shown in Figures 1 and 2, respectively. These graphics display a consistent trend of decreased scores (ie, improvement) in both pain and stiffness over time from baseline through week 25.

Additional analyses of the Phase I data were conducted by using a responder definition of 30% change in each NRS score from baseline to week 25; the proportion of responders for the pain and stiffness end points were calculated. Of the 15 participants with both baseline and week 25 NRS data, 10 (66%) were responders for the pain end point, and 11 (73%) were responders for stiffness. Of all participants with baseline NRS data (including dropouts and incompletes at week 25; n = 23), 43% were responders for pain, and 48% were responders for stiffness.

Scatterplots of change in NRS scores according to change in tumor size for patients with baseline and week 25 data are shown in Figures 3 and 4. These figures suggest a strong relationship between the radiologic outcome (tumor size change) and the patient-reported pain and stiffness outcomes in the Phase I data.

DISCUSSION

To our knowledge, this study is the first to gather information directly from patients with TGCT regarding the disease-specific symptoms and effects associated with the condition. The study was motivated by the need to support and complement the meaningfulness to patients of changes in a clinical/radiologic end point (ie, tumor volume) in response to a novel treatment. In a disease such as TGCT, which is rarely lethal and where the affected population is generally younger than in many other malignancies that result in death, systemic treatment could be given for years; thus, understanding the impact of therapies and the relevance of treatment outcomes to patients' quality of life is essential.[11]

The results from this study suggest that pain, swelling, and stiffness are the most common and important symptoms from the perspective of patients with TGCT. Reduced range of motion, instability, giving out, and catching were also commonly mentioned. Patients reported a wide range of effects on their physical functioning as a consequence of these symptoms. These findings are consistent with clinical expert input regarding important TGCT symptoms and effects. It is interesting to note that, because TGCT is a rare condition, even the clinical experts were unable to provide a sufficiently comprehensive and specific characterization of the disease and its effects to confidently select PRO measures without gathering input directly from patients.

Although there were symptoms that emerged as clear hallmarks of the disease, there was evidence of variability in the symptom experience. Not all patients experience all symptoms (eg, swelling but not pain, or pain and swelling but not stiffness or reduced range of motion). There is also variability in how patients experience the symptoms within and among days. The evidence of variability based on the descriptions provided by patients reflects the need for brief recall periods in assessing these symptoms. Not all of the symptoms may be best assessed through patient self-report; for example, swelling may be best measured

morphometrically in the clinic. Clinical measurement of swelling is likely to be more objective; in addition, several of the patients reported that swelling as a symptom was relevant to them primarily because of the consequent pain, stiffness, or impairment in physical functioning. The sample for this study included participants with active disease and others who had previously resected tumors; however, no differences were noted in the concept elicitation or cognitive debriefing results based on tumor status (Table III).

Patients reported a range of limitations to their physical functioning as a consequence of their TGCT that varied depending on the location of the tumor. This scenario presented a challenge in identifying an instrument that would cover the range of effects associated with multiple, different tumor locations (ie, upper extremity vs lower extremity). Selection of a subset of the items from the PROMIS-PF item bank, with 1 item set for the upper extremity population and a second item set for the lower extremity population, was informed both by direct patient input and with consideration for the statistical properties of the individual candidate items. The item-specific characteristics were available on the PROMIS website and were estimated by the developers by using item response theory. This approach provides the flexibility needed to assess a common concept (ie, impact on physical functioning), using a common metric (ie, a latent physical functioning trait), in a heterogeneous sample of patients. These 2 PROMIS-PF item subsets have been included as outcome measures in the ongoing Phase III clinical trial of patients with TGCT (NCT02371369).

We used literature reviews, clinical expert input, direct interviews with patients, and existing banks of items with known measurement properties to select subsets of items appropriate for the measurement of a single concept (physical functioning) in a heterogeneous population of patients. This measurement approach may be particularly appealing to researchers in oncology who encounter similar rare and/or heterogeneous populations in their research; for example, in studies of rare conditions in which subgroup analyses are either infeasible or impractical.

This approach is only feasible when there are existing item banks for the concept of interest that include high-quality and well-characterized items. PROMIS investigators followed standardized and rigorous methods to develop the repository of physical functioning items that can be administered as a tailored tool for the population of interest. Development of the PROMIS-PF item bank involved the initial identification of 1860 items.[22] The best-fitting PROMIS-PF items were selected by using item response theory and confirmatory factor analysis, yielding an item bank of the most relevant, clearest, and best understood items. The use of the PROMIS-PF item bank in the manner described is consistent with one of the stated objectives of the National Institutes of Health PROMIS Initiative, which is to establish a national resource for accurate and efficient PRO measurement.[23]

In testing, developing, and using PRO instruments in a novel treatment development process, it is important to follow guidance on PRO measures issued by the US Food and Drug Administration (FDA) and the European Medicines Agency[24,25] and to engage with regulatory agencies early. The recommendations in the FDA's PRO guidance, which are labeled by the FDA as nonbinding, may be viewed as challenging and unrealistic for those studying rare diseases. The approaches taken in the present study offer some viable

alternatives to the more direct and comprehensive approaches that are only feasible with more common diseases. Some examples of these alternatives are: (1) review of the literature and existing PRO measures (eg, PROMIS-PF item bank) from other disease areas in which there are relevant parallels between patients' experiences of symptoms and effects (ie, literature for osteoarthritis, rheumatoid arthritis, and meniscal tears); (2) soliciting additional input from clinical experts to guide the research and support content validity when the ability to gather input directly from patients is limited; and (3) a greater degree of flexibility in recruitment and interviewing methods and in determination of acceptable sample sizes given the difficulties of conducting research in rare diseases. The exact methodology for gathering and summarizing evidence to support the use of PROs is not detailed but is broadly discussed in the FDA guidance. In addition, the experience of our team with this particular study of TGCT suggests that there is flexibility and understanding on the part of regulators in the determination of acceptable approaches and methodologies for gathering reasonable evidence. For this particular program of research, interactions with regulatory agencies were helpful in selecting appropriate end point concepts and measures, positioning of the PROs in the end point hierarchy, and reaching agreement on the appropriate methods for the analysis of the data. There is also value in communicating with regulatory agencies early on and regularly throughout the development process; thus, any issues can be discussed and addressed, in particular where consideration for the challenges associated with conducting research in rare diseases is warranted.

Various limitations of this study merit mention. Our recruitment strategy included the identification of patients through online blogging and website posts. This approach introduces a potential selection bias in that individuals who blog and post online may be systematically different in terms of their symptom experiences from those who do not interact online. Our online recruitment efforts resulted in the identification of only female subjects; recruitment from clinical sites was necessary to identify male participants with TGCT. There were no apparent differences between the sexes in their reports of the symptoms or effects of TGCT. Recruitment of patients with a rare disease can be extremely challenging. The recruitment methods used in this study, although not without inherent limitations, were used to successfully recruit an adequate sample of patients with consideration for practical issues relevant to all research, namely time and financial constraints. This recruitment strategy may be an acceptable primary or supplementary strategy in future studies of similarly rare disease populations. Although some participants were interviewed in-person while others were interviewed over the telephone, we found no specific differences in the nature or quality of the information gathered. This outcome suggests that telephone interviews may be an acceptable approach for interviewing patients with rare conditions when access to patients across a large geographical area presents a significant challenge. An additional limitation is that 5 participants did not have a clinician-confirmed diagnosis of TGCT; however, comparison of the results across the 2 groups did not suggest any noticeable differences. Finally, we were unable to recruit a sample of patients representing all bodily locations that can be affected by TGCT. For example, no patients experienced a tumor in the jaw or spine, and only 2 tumors were located in the upper extremities. As a consequence, there were some assumptions made about the nature and extent of the effects of TGCT on physical functioning for patients with upper extremity

tumors; this may be an area for further research. It is important to note, however, that the distribution of upper versus lower extremity tumors in our sample (ie, ~90% lower extremity) is consistent with the prevalence in the target population, in which a high percentage of the tumors affect large joints, especially the knee.[2]

We encourage replication of the methods reported in this study toward the goal of meeting the need to identify relevant PRO measures for other oncology indications. The approach taken for this study allowed for the identification of existing PRO measures from other therapeutic areas and the adaptation and application of those measures, as appropriate, for TGCT. Use of the NRS items that were adapted for the Phase I clinical trial of pexidartinib is supported by the data presented herein, which suggest a strong relationship between the clinical/radiologic outcome (tumor size change) and the NRS patient-reported pain and stiffness outcomes. Areas for future research in TGCT include an exploration of the relationships between PROs and other clinical factors such as bulk of disease, past procedures, tumor location, duration of disease, tumor size, and analgesic medication use. Data from the ongoing Phase III trial of pexidartinib (NCT02371369) among patients with TGCT may provide an opportunity to investigate these relationships and may provide additional insights into the value and appropriate use of PRO measures in this rare disease patient population. In addition, further evaluation of the content validity of the selected PROMIS-PF items is ongoing.

CONCLUSIONS

This study is the first, to the best of our knowledge, to gather information directly from patients with TGCT regarding their symptom experiences. The findings of this study show that several PRO instruments may be useful in assessing the effects of treatments for TGCT from the patient perspective. Based on the results, the pain and stiffness NRS items and specifically tailored PROMIS-PF PROs have been identified as the most appropriate measures. In a Phase I trial, the pain and stiffness PRO measures were included on an exploratory basis, and early results suggest that they effectively measure improvements from the patient perspective. These instruments are being incorporated into a Phase III clinical trial as important secondary end points to support the meaningfulness of reduction in tumor volume.

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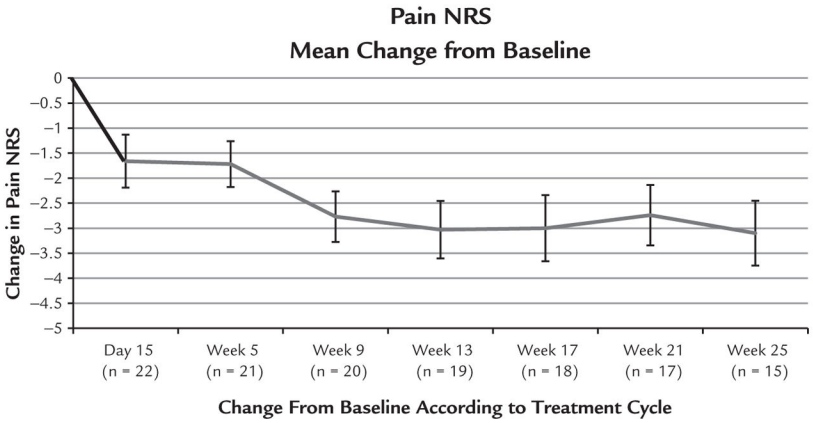

Figure 1.
Mean change from baseline: pain numeric rating scale (NRS).

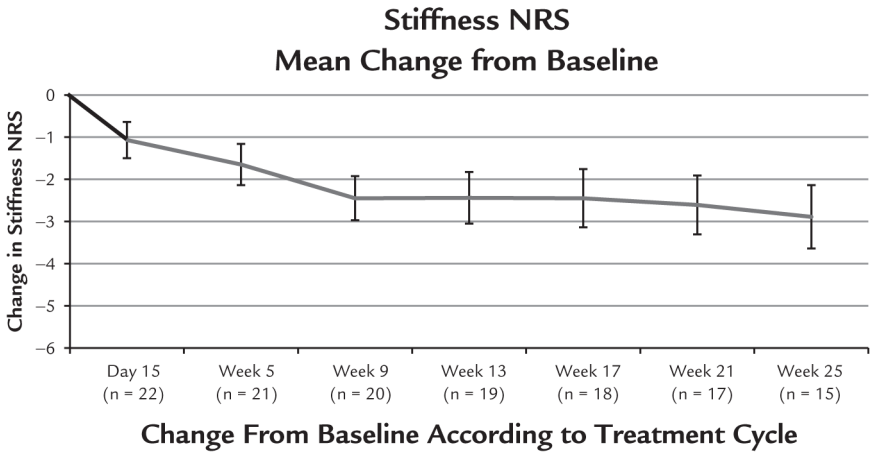

Figure 2.
Mean change from baseline: stiffness numeric rating scale (NRS).

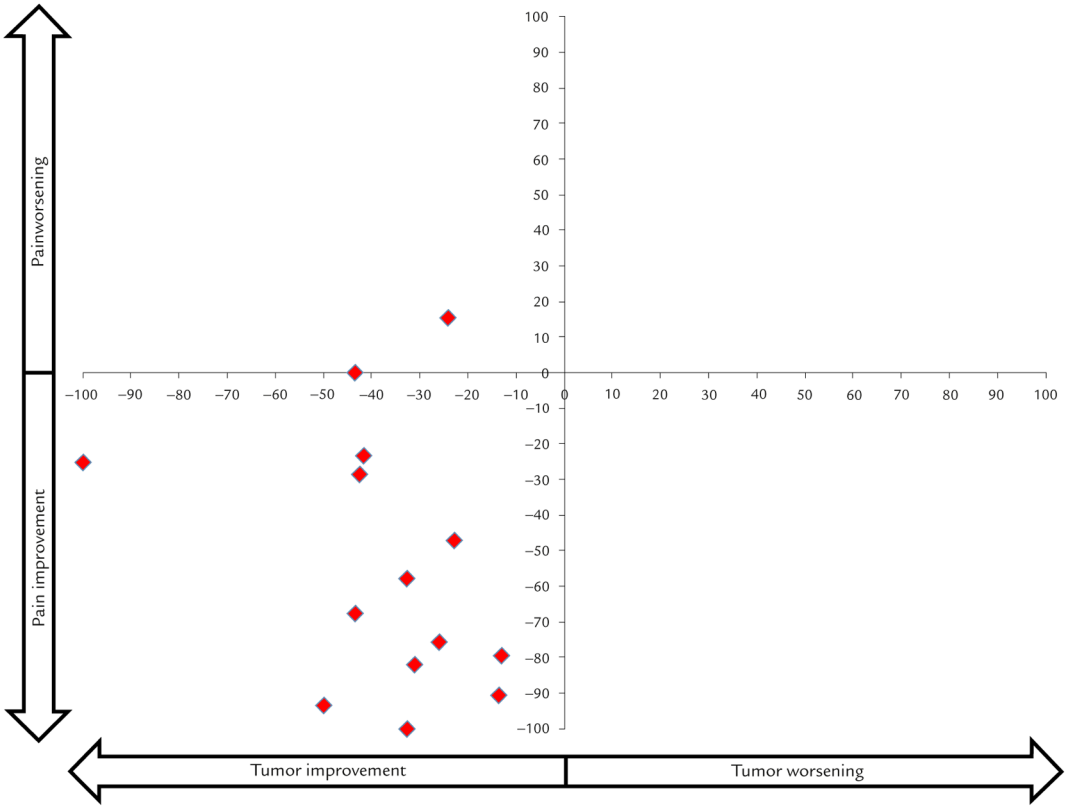

Figure 3.

Scatterplot of percent change in tumor size according to percent change in numeric rating scale pain score: baseline to week 25. Tumor size was assessed by using local Response Evaluation Criteria in Solid Tumors version 1.1 guidelines.

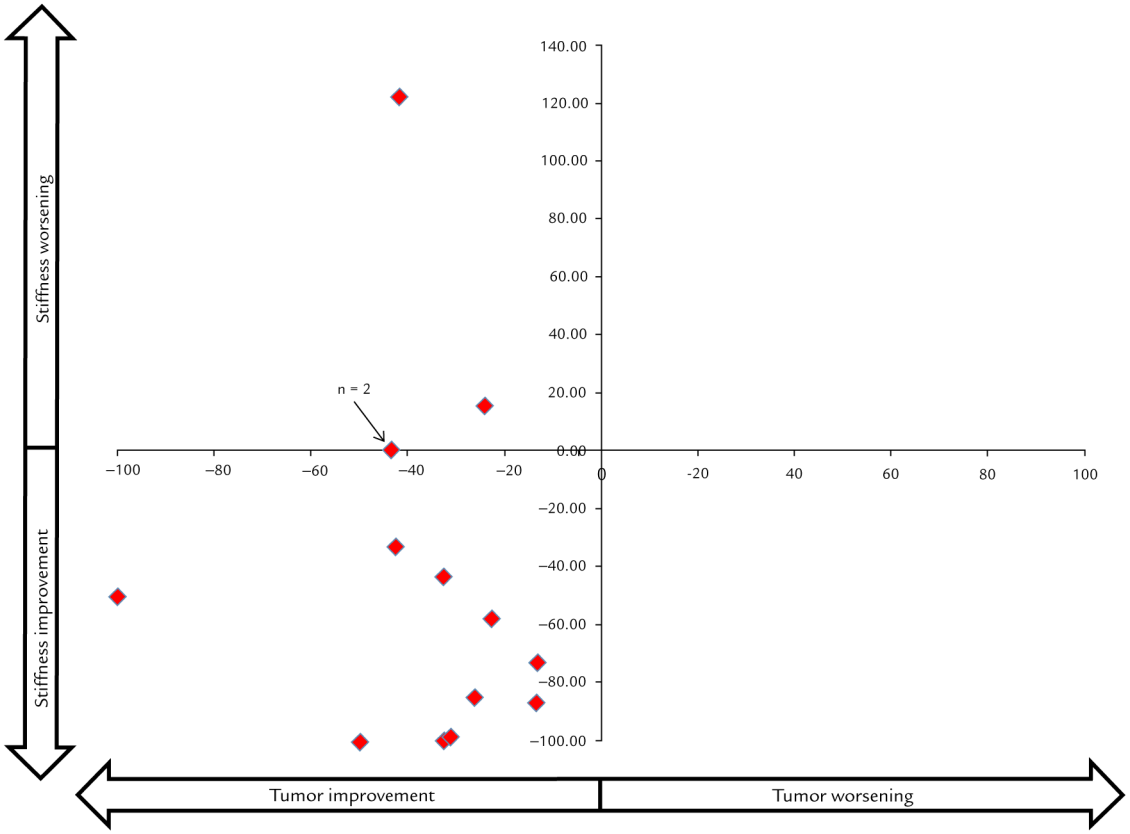

Figure 4.

Scatterplot of percent change in tumor size according to percent change in numeric rating scale stiffness score: baseline to week 25. Tumor size was assessed by using local Response Evaluation Criteria in Solid Tumors version 1.1 guidelines.

Table I

Participant-reported sociodemographic characteristics. Unless otherwise indicated, values are given as no. (%).

Characteristic	Full Sample (N = 22)
Age, y	
Mean (SD)	42.5 (9.0)
Median (minimum–maximum)	44.0 (27–56)
Male	6 (27)
Hispanic or Latino	2 (9)
Race *	
White	21 (95)
Black or African American	0
Asian	0
Native Hawaiian or other Pacific Islander	0
American Indian or Alaskan Native	0
Other	1 (5)
Marital status	
Married	15 (68)
Single	7 (32)
Divorced/separated	0
Widowed	0
Other	0
Employment status	
Employed, full-time or part-time	13 (59)
Homemaker	3 (14)
Student	2 (9)
Unemployed	3 (14)
Retired	0
Disabled	1 (5)
Education	
Elementary/primary school	0
Secondary/high school	0
Some college	4 (18)
College degree	15 (68)
Postgraduate degree	3 (14)
Technical or vocational degree	0
Other	0

* = options are not mutually exclusive.

Table II

Participant-reported clinical characteristics. Values are given as no. (%).

Characteristic	Full Sample (N = 22)
Type of tumor	
PVNS	19 (86)
GCT-TS	3 (14)
>1 joint affected	0
Location of tumor	
Knee (any region)	15 (68)
Knee (anterior)	4 (18)
Knee (anterior and posterior)	8 (36)
Knee (posterior)	2 (9)
Knee (anterior and posterior and side)	1 (5)
Hip	3 (14)
Ankle	2 (9)
Foot	0
Shoulder	0
Elbow	1 (5)
Hand	0
Wrist	0
Other*	1 (5)
Known procedures and medications to treat tumor†	
Synovectomy	13 (59)
Arthroscopy	11 (50)
Other surgery type‡	10 (45)
Drainage	6 (27)
Other§	8 (36)
Narcotics	2 (9)
Anti-inflammatory drugs	8 (36)
Steroids	2 (9)

GCT-TS = giant cell tumors of the tendon sheath; PVNS = pigmented villonodular synovitis.

*Other area is forearm.

†Options are not mutually exclusive.

‡Other surgery types specified by study participants included: “first time may have been synovectomy” (1); “six ankle surgeries” (1); “anterior cruciate ligament replacement due to tumor damage” (1); “began as arthroscopy then opened me up to remove the tumor” (1); “tumor removal” (1); “total knee replacement” (3); “hip replacement” (1).

§Other procedures specified included: biopsy; cortisone injection; radiation; external beam radiation therapy; injected radiation; left total hip replacement 12-4-12; tumor removed surgically off of artificial joint site; and reported radiation beam.

Table III

Patient-reported symptoms of tenosynovial giant cell tumor.

	Tumor Present at Time of Interview											Tumor Resected, Not Present at Time of Interview											Total (N = 22)
Participant ID No.:	**008**	**001**	**007**	**015**	**016**	**017**	**018**	**019**	**024**	**022**	**025**	**002**	**004**	**005**	**006**	**010**	**011**	**012**	**014**	**020**	**021**	**023**	
	L	**R**	**L**	**L**	**R**	**R**	**R**	**L**	**L**	**R**	**L**	**L**	**L**	**L**	**L**	**R**	**L**	**L**	**L**	**R**	**L**	**R**	
Tumor Location:	**knee**	**knee**	**elbow**	**ankle**	**knee**	**knee**	**knee**	**knee**	**knee**	**knee**	**knee**	**hip**	**hip**	**knee**	**knee**	**knee**	**knee**	**knee**	**ankle**	**knee**	**hip**	**forearm**	
Physician-confirmed diagnosis:	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**		**Yes**	**Yes**			**Yes**	**Yes**	**Yes**			**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	
Pain																							
Pain	S	S	S	-	S	S	S	S	S	S	-	S	S	S	-	S	S	S	P	S	S	-	18
Swelling	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Swelling	S	S	P	S	S	S	S	S	S	S	P	S	-	S	S	P	S	-	P	S	-	P	19
Limited motion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stiffness/tightness	P	-	P	P	P	S	S	-	P	S	P	S	S	S	P	-	S	P	-	-	-	P	16
Reduced ROM problems with extension/ flexion	-	-	S	S	-	S	S	S	S	S	S	-	S	S	S	-	S	-	S	-	-	P	14
Instability																							
Giving way/out	-	S	P	-	S	-	S	S	-	-	-	-	S	S	-	P	P	S	P	P	S	P	14
Instability	P	P	P	P	-	-	P	P	-	-	P	-	P	P	-	-	S	P	S	-	-	-	12
Terms related to ease of movement																							
Catching	S	-	P	-	-	P	-	P	-	P	-	S	P	P	P	P	P	S	-	P	P	-	14
Locking	S	-	S	-	-	P	-	-	-	-	-	P	-	-	-	-	S	S	-	-	-	-	6
Sound during movement																							
Popping	S	S	-	S	-	P	-	S	-	-	-	S	P	S	S	P	P	S	-	-	-	-	12
Clicking	S	S	S	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-	-	4
Grinding	-	-	-	-	-	-	S	-	-	-	P	S	-	-	-	-	-	-	-	-	-	-	3
Snapping	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	P	-	-	-	-	-	-	2
Cracking	-	-	-	S	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	2
Other symptoms/terms[†]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pressure	-	S	S	-	-	-	-	-	S	S	-	-	-	-	S	-	-	-	-	-	-	S	6
Weakened/tired/lack of strength in muscles	-	-	-	-	-	-	-	-	-	S	P	-	-	S	S	-	-	-	-	-	-	S	5
Heat, hot to touch	-	-	S	-	-	-	-	S	-	-	-	-	-	S	-	-	S	-	S	-	-	-	5
Sensitivity/Discomfort	-	-	-	-	-	-	S	-	-	S	-	-	-	S	-	-	-	-	S	-	-	-	4

	Tumor Present at Time of Interview											Tumor Resected, Not Present at Time of Interview											Total (N = 22)
Participant ID No.:	**008**	**001**	**007**	**015**	**016**	**017**	**018**	**019**	**024**	**022**	**025**	**002**	**004**	**005**	**006**	**010**	**011**	**012**	**014**	**020**	**021**	**023**	
	L	**R**	**L**	**L**	**R**	**R**	**R**	**L**	**L**	**R**	**L**	**L**	**L**	**L**	**L**	**R**	**L**	**L**	**L**	**R**	**L**	**R**	
Tumor Location:	**knee**	**knee**	**elbow**	**ankle**	**knee**	**knee**	**knee**	**knee**	**knee**	**knee**	**knee**	**hip**	**hip**	**knee**	**knee**	**knee**	**knee**	**knee**	**ankle**	**knee**	**hip**	**forearm**	
Physician-confirmed diagnosis:	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**		**Yes**	**Yes**			**Yes**	**Yes**	**Yes**			**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	
Enlargement (solid)/cyst	-	-	-	S	-	-	-	-	S	-	S	-	-	-	-	-	-	-	-	-	-	-	3

L = left; R = right; ROM = range of motion.

*Symptoms that arise spontaneously are often the most relevant and severe; these are indicated by an “S.” Symptoms that participants indicated that they had experienced only after probing from the interviewer are noted by a “P.” Symptoms not endorsed as part of the participant’s experience either spontaneously or after probing are indicated by a “-”.

†Other symptoms reported by 1 participant each included: pulsating sensation, knot, cramps, rash/itchiness, irritated muscles, numbness, and fatigue/tiredness.